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REVIEW ARTICLE

Role of Surgery in the Management of Postmastectomy Extremity Angiosarcoma (Stewart-Treves Syndrome)

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Stewart-Treves syndrome (STS) is the rare occurrence of angiosarcoma in a setting of postmastectomy upper extremity lymphedema. A collective comparison of outcomes following various initial treatment options in STS has not previously been reported. We reviewed 160 cases of STS reported in the literature since 1966. We analyzed the relationship between initial treatment and survival in all 92 of these patients for whom detailed treatment and outcome data had been reported. There was no significant difference in survival comparing those initially treated with wide excision (n = 16) and those treated with amputation (n = 45) ($P = 0.40$). Even in the setting of initial surgical treatment, overall long-term survival was poor (<40%). There have been even fewer long-term survivors among those treated initially with regional chemotherapy (n = 7) or radiation therapy (n = 24). An update on STS and a discussion of recent advances in the understanding of its molecular pathogenesis that may result in future treatment improvements are presented.

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KEY WORDS: postoperative complications; lymphedema; radiotherapy; drug therapy; mastectomy; hemangiosarcoma

INTRODUCTION

Our recent experience with a case of Stewart-Treves syndrome (STS) led us to investigate treatment options. The features of presentation of this 76-year-old female patient were illustrative of STS. This patient had undergone a right modified radical mastectomy 22 years prior to her presentation for a T1N0M0 breast cancer. Eight years following her mastectomy (14 years prior to presentation), she developed a new right axillary mass. She underwent excision of the right axillary mass, which showed recurrent breast carcinoma and was subsequently treated with 5,000 cGy to the right axilla. At the time of admission, she related a history of right upper extremity lymphedema that had been present for 20 years. She was admitted with increasing swelling and skin changes of her right upper extremity, which were thought to be cellulitis (Fig. 1). At the time of surgical consultation, she had been receiving intravenous (IV) antibiotics for 1 week for cellulitis. This bedridden elderly female had marked edema of the right upper extremity extending to the shoulder area. On the dorsum of her right forearm was an area with multiple irregular dark purple nodules. The possibility of Stewart-Treves tumor was raised. His-

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Fig. 1. **A:** Appearance of lesions on forearm in our patient with Stewart-Treves syndrome. **B:** Close-up view of lesions from the same patient.

tology of lesional biopsies was consistent with angiosarcoma, or STS (Fig. 2). Both patient and family declined all but supportive care.

Lymphedema following axillary lymph node dissection has been reported to occur in 8% to 35% of patients [reviewed in 1]. The most feared complication of postmastectomy lymphedema is angiosarcoma occurring in the affected extremity. Since the association between postmastectomy lymphedema and angiosarcoma (STS) was made by Stewart and Treves at Memorial Hospital in 1948 [2], this clinical entity has been reported in over 300 cases [3]. It has been estimated to occur in between 0.07% and 0.45% of patients after axillary dissection for breast cancer [3].

Past treatment recommendations for STS have been based on anecdotal experiences or small, individual institutional experiences. To better understand the natural history of STS following a variety of initial treatment options, we analyzed treatment and outcome data available on cases reported since 1966.

MATERIALS AND METHODS

Reported cases of STS were collected from a Medline (1966–1998) search using a combination of the key words "Stewart-Treves syndrome," "angiosarcoma," "lymphangiosarcoma," "extremity sarcoma," "lymphedema," "mastectomy," "chemotherapy," "radiation therapy," and "surgery." Patients included in the analysis came from reports [3–21] in which information on initial treatment and follow-up were available for all patients. For the purposes of this study, STS refers to the devel-

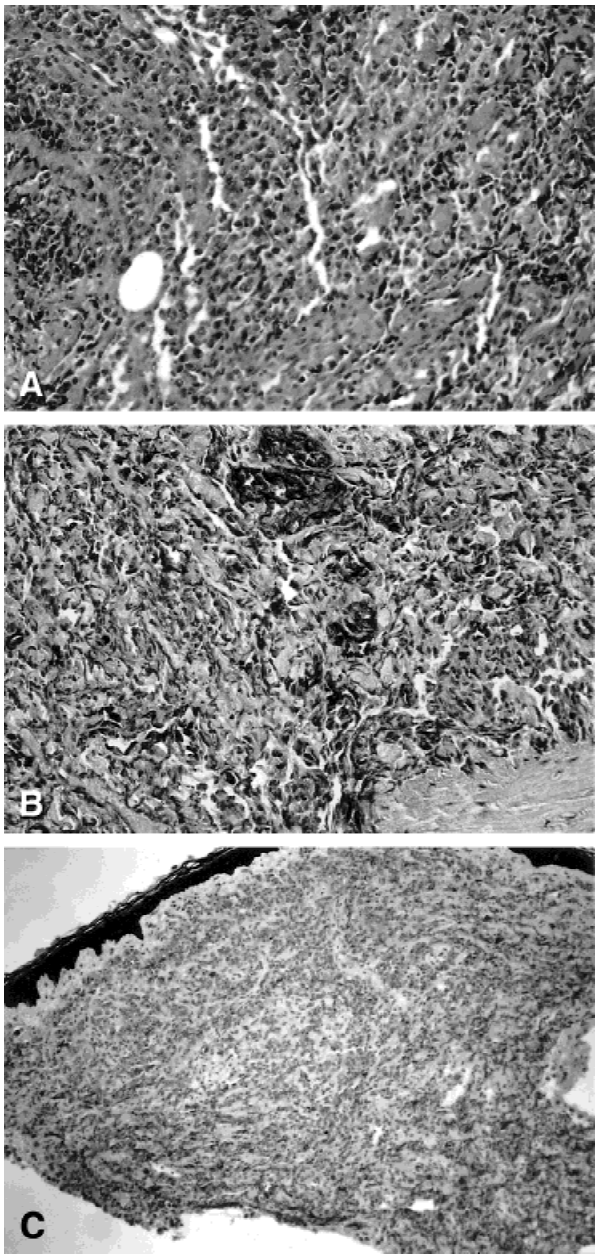

Fig. 2. Histological appearance of Stewart-Treves syndrome. **A:** High-power photomicrograph of dermal infiltrative tumor with large pleomorphic cells arranged in trabeculae and occasionally lining slit-like spaces. **B:** High-power photomicrograph of dermal tumor revealing focal positivity for factor VIII–related antigen by immunoperoxidase staining. **C:** Low-power photomicrograph of skin with epidermis, which is keratin-positive by immunoperoxidase staining, and the underlying dermis with infiltrative tumor, which is keratin-negative.

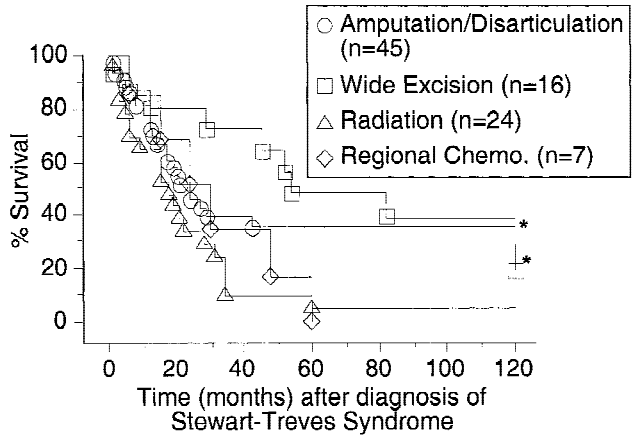

Fig. 3. Survival following most commonly reported therapies used in the treatment of postmastectomy angiosarcoma arising in a lymphedematous upper extremity. Survival curves based on 92 cases in the literature since 1966 for which initial treatment and follow-up data were available. Kaplan-Meier disease-specific survival curves are shown (symbols represent event times); log-rank test was used to determine significance. *$P < 0.04$ compared to radiation therapy or regional chemotherapy. There was no statistically significant difference between survival following wide excision compared with amputation.

opment of angiosarcoma in a lymphedematous extremity following mastectomy. Patients who had angiosarcoma arising in lymphedema not in the postmastectomy setting were excluded. Disease-specific survival data for the 4 most commonly reported initial treatment modalities (amputation or disarticulation, wide excision, external beam radiation, and regional chemotherapy) were analyzed as Kaplan-Meier curves. Survival was compared with the log-rank test using StatView (Abacus Software, Berkley, CA). A P value <0.05 was considered statistically significant.

RESULTS

We identified 160 cases of STS reported in the literature since 1966. Data sufficient for analysis were available on 92 patients (Fig. 3). All patients included in the analysis were female, and there was no difference in age among the patients in the different groups: amputation, 63.4 ± 1.6 years, $n = 45$; wide excision, 65.3 ± 2.4 years, $n = 16$; radiation, 69 ± 4 years, $n = 24$; regional chemotherapy and patient age were given in only 1 of 7 cases [12,21].

Either initial amputation or disarticulation ($P < 0.04$) or wide excision ($P < 0.03$) provided statistically significant better survival than did radiation therapy or regional chemotherapy. There was no statistically significant difference in survival when those initially treated with amputation were compared to those initially treated with wide excision ($P = 0.40$). There was no statistically significant difference in survival in those treated with radiation compared to those treated with regional chemotherapy ($P = 0.44$).

A high rate of subsequent extremity amputation following wide local excision did not account for its overall efficacy. In the initial wide excision group ($n = 16$), 6 patients survived beyond 5 years. Among these 6 patients, additional therapy for management of the angiosarcoma consisted of amputation, 1 case; radiation therapy, 2 cases; and no further therapy, 3 cases.

DISCUSSION

Lowenstein is reported to have first described lymphangiosarcoma in a patient with upper extremity lymphedema in 1906 [10]. In 1948, Stewart and Treves [2] reported 6 cases of lymphangiosarcoma in postmastectomy lymphedema. It is now estimated that 10% of angiosarcomas occur in association with chronic lymphedema, and in a majority of cases, this lymphedema occurs in the postmastectomy setting [22]. Other causes of lymphedema that have been reported in association with angiosarcoma include Milroy's disease [23], radiation [24,25], lymphedema secondary to trauma [22,26], lymphedema secondary to vascular stasis [27,28], filarial infection [29], and idiopathic acquired lymphedema [30]. Edema secondary to cardiac, renal, or hepatic disease has not been associated with the development of angiosarcoma [30]. Sarcomas other than angiosarcoma have been reported to occur in the axilla, shoulder, chest wall, and supraclavicular regions following mastectomy and radiation therapy [31]. These tumors are thought to be radiation-induced sarcomas [31,32] and, thus, to be distinct in etiology from those observed in postmastectomy lymphedema. Axillary radiation is contributory to the development of STS by compounding or precipitating postsurgical lymphedema [3,33,34] (see below).

The etiology of angiosarcoma arising in lymphedematous extremities has been the subject of much speculation, most of which is of primarily historical interest [35]. There is experimental evidence that the development of malignancy in lymphedematous extremities is facilitated by lymphedema-induced alterations in immune function [reviewed in 6; 36,37]. Stark et al. [38] demonstrated delayed rejection of homograft skin in lymphedematous arms compared to normal arms. More recently, Mallon et al. [39] demonstrated altered cell-mediated immunity in the arms of patients with postmastectomy lymphedema. If this hypothesis is correct, prevention of lymphedema should reduce the incidence of postmastectomy extremity angiosarcoma [10,12,15]. Breast conservation therapy, including lumpectomy and axillary sampling, and the avoidance of the combination of axillary dissection and axillary radiation have been associated with decreased rates of lymphedema and may lead to a decrease in the incidence of STS [40,41]. The increased application of sentinel node biopsy in the staging of breast cancer may also ultimately lead to a reduction in the incidence of postmastectomy lymphedema and extremity

angiosarcoma [42]. Adjunctive measures to reduce lymphedema should be employed in affected patients as they may reduce risk [6,10,13,15,43].

By light microscopy, the histological appearance of angiosarcoma is variable [7]. It may appear as well-developed, erythrocyte-containing, capillary-like vessels or as poorly differentiated, abortive vascular formations of various sizes (Fig. 2A). Other areas may appear as loosely arranged sheets of cells [7,8]. Angiosarcomas have been demonstrated to have a prominent proliferation of reticular fibers in association with the tumor [7,13,28]. Positive staining for factor VIII Rag (Fig. 2B), laminin, CD31, vimentin, and collagen IV as well as binding of *Ulex europaeus* I lectin may help identify tumors as angiosarcomas [7,8,44–47]. There has been controversy surrounding the cellular origin of angiosarcomas. The general term "angiosarcoma" has been used to describe tumors arising from blood and/or lymphatic vessels due to difficulties in discrimination of vascular and lymphatic endothelium by light microscopy [28,48]. The recently described blood vessel endothelium-specific marker *Psophocarpus tetra* gonolobus agglutinin [8] and the lymph-specific markers podoplanin [49] and vascular endothelial growth factor receptor-3 [50] may contribute to a better understanding of the genesis of these tumors.

The lesions in STS typically appear as "a slightly raised, macular or polypoid lesion . . . a solitary tumor followed by similar satellite areas that sometimes become confluent, forming a larger lesion" [2] (Fig. 1A, B). These blue-reddish nodules commonly bleed [11]. The appearance of these lesions is often misleading to both patients and clinicians. Reported initial findings have included rapid arm swelling [22], expanding plaques [2], bruising [13,15], and increasing pain [51]. Reported initial diagnoses of lesions later found to be angiosarcoma include Kaposi's sarcoma [22], cellulitis [22,52], recurrent breast cancer [5], and gangrene with superinfection [6,53]. In angiosarcoma arising in postmastectomy lymphedema, approximately two-thirds of the lesions occur on the arm [14,33]. The lesions have been reported to occur less commonly on the forearm, elbow, shoulder, and hand [14,33].

Early diagnosis is essential to the survival of patients who develop STS [14,34]. Woodward et al. [14] found that long-term survivors had an average time of 5.6 weeks between onset of lesions and amputation compared with an average of 24 weeks for nonsurvivors. In light of the diversity of presentations of angiosarcoma and the importance of early diagnosis, any suspicious lesion in a lymphedematous arm requires multiple deep biopsies [10,54]. Fine-needle aspiration is not adequate for establishing the diagnosis [55].

The average age of patients with STS in this study was 65.5 ± 1.2 years. This is approximately 10 years older than the average age of patients who develop angiosarcoma in chronic lymphedema not secondary to mastectomy [34]. STS has been reported to occur in a male [56]. It has been reported to occur in white [2], black [5], and Asian [33] women.

STS occurs on average 10–11 years (range 1–30) following mastectomy [14,33,57]. Upper extremity lymphedema has been estimated to occur on average 9 years prior to the development of angiosarcoma [33]. Nearly all reported cases of upper-extremity angiosarcoma developing after mastectomy occurred in the setting of lymphedema; however, cases of angiosarcoma occurring after mastectomy have been reported in nonlymphedematous arms [33]. There is no relationship between the primary pathology of the breast lesion and the development of angiosarcoma [33]. Angiosarcoma has been reported in the setting of upper-extremity lymphedema following axillary dissection for benign breast pathology [2]. Axillary nodal positivity at the time of axillary dissection is not associated with an increased incidence of STS [14,27]. Between 35% [34] and 90% [14] of patients in different series have had radiation following mastectomy and prior to the development of angiosarcoma.

Prospective randomized trials considering all extremity sarcomas as a group have demonstrated that radical surgery offers no survival advantage over wide local excision [reviewed in 58]. Two biological properties, a propensity for lymph node metastasis [59] and multifocality [4,7,60], have led some authors to question whether lessons learned from these trials are applicable to extremity angiosarcoma [4,61]. In addition, others [7,14,27,34] have recommended amputation for STS based solely on single-institutional experiences.

In most reports on STS, authors have failed to provide staging information on tumors or the rationale behind management decisions. The results of the present retrospective study must be interpreted with caution. We cannot exclude the possibility in the present study that observed differences in outcome are solely a function of early-stage tumors being treated with surgery and late-stage tumors being treated with radiation or chemotherapy. In addition, the small sample sizes of the study groups limit the power of the present observations. A complete comparison of management options in STS would require a prospective randomized trial, as has been done for all cases of extremity sarcoma. The rarity of STS and the poor overall prognosis of patients with STS make such a trial unlikely.

The present results show that initial wide excision is equivalent to amputation in the management of STS. Wide excision, thus, may be considered in those with STS in whom excision can be accomplished with clear margins. Wide excision in STS should be done, as in other extremity sarcomas, with a 2–3 cm margin of normal tissue when possible [reviewed in 58]. Involvement

of bone, major nerve structures, and vascular structures should remain a relative indication to proceed with amputation [58].

While there are reports of long-term survivors with external beam radiation therapy [62] and with administration of intraarterial radioactive yttrium [63], radiation therapy has not been very effective at improving overall long-term survival in patients with STS. This is supported by the results of the current analysis (Fig. 3). Woodward et al. [14] similarly found a lack of efficacy of radiation therapy compared to amputation in patients treated before 1972. Radiation therapy has been used primarily as an adjunct to surgery and/or chemotherapy [4,5,10,31]. Prospective randomized studies in extremity sarcoma have found that radiation therapy, either external beam or brachytherapy, improves local control of disease, though it has not been shown to improve overall survival [64,65]. We are aware of no reports of brachytherapy in STS.

While there have been anecdotal reports of long-term survivors following systemic chemotherapy [12] and regional chemotherapy [3,66] in STS, overall there has been limited success at treating STS with chemotherapy [12]. As a result, chemotherapy with or without radiation therapy has been reserved for patients who present with inoperable disease, who develop inoperable recurrences, or who have refused amputation [12]. Yap et al. [12] reported a partial response in 7 and a complete response in 1 of 19 therapeutic trials of chemotherapy in 11 patients with STS. The median duration of response was 6 months. They further found response to any 1 systemic chemotherapeutic agent was associated with significantly prolonged survival. Systemic chemotherapeutic agents generating a response have included methotrexate, 5-fluorouracil, doxorubicin (Adriamycin) combined with dacarbazine, and actinomycin D [10,31,67]. Trials with regional chemotherapy have met with only limited success [12,21] (Fig. 3). Although interleukin-2 has been reported to have some efficacy in STS [68], a recent Japanese study showed no improvement in outcome of patients treated with interleukin-2 [67].

Reported mean survival for patients with STS is 20 months [45]. Length of survival in untreated patients is 5–8 months [14,45]. Planning of appropriate therapy for these patients hinges on the presence or absence of metastatic disease at the time of presentation. Metastatic disease should preclude the use of surgical therapy except in situations where it may be useful for symptomatic improvement. While magnetic resonance imaging has been recommended to assess the local extent of extremity sarcomas [58], some authors have questioned its value in delineating the margins of the tumor in STS [4]. Chest computed tomography scanning should be employed to assess the presence of pulmonary metastasis [31,58]. Lymphangiography was reported to be of no value in the assessment of the extent of disease in angiosarcoma [33]. As somatostatin and vasoactive intestinal peptide (VIP) receptors have recently been identified in angiosarcomas [69], somatostatin and/or VIP receptors may be future targets for in vivo imaging and staging. Positron emission tomography scanning is currently being evaluated for use in the assessment of primary lesions and in the detection of metastatic disease [70,71].

Developments in understanding the molecular pathogenesis of angiosarcoma may provide new options in the treatment of patients with STS. *p53* is a tumor-suppressor gene that has been studied extensively in human malignancy [reviewed in 72]. The finding that *p53*-deficient mice develop spontaneous angiosarcomas first suggested that defects in the *p53* systems might be important in the development of human angiosarcomas [73]. Human angiosarcomas have a high rate of *p53* mutations and a high level of expression of murine double-minus-2 (MDM-2) protein, a negative regulator of wild-type *p53* [74]. Interest has recently developed in the use of antiangiogenesis therapy in the treatment of solid tumors [reviewed in 75]. This therapy is based on the principle that solid tumors >2–3 mm require recruitment of a new blood supply to sustain growth [76]. Vascular endothelial growth factor is an endothelial cell mitogen and is among the most potent stimulators of angiogenesis [77]. Analysis of angiosarcomas by immunohistochemistry has demonstrated high levels of vascular endothelial growth factor compared to benign vascular lesions [74]. In cases in which vascular endothelial growth factor is identified, expression of its receptor has also been identified [78].

Prognosis in STS is not significantly associated with age, site of occurrence [14,27], or length of time between mastectomy and disease [14]. The relationship of tumor size to survival has not been established in STS; however, small tumor size (<5 cm) in face and scalp angiosarcomas has been associated with improved survival [27]. Death from STS usually occurs as a result of pulmonary metastases [11,30,79]. Metastases may also occur to bone and liver [34].

In conclusion, extremity angiosarcoma occurring in the setting of postmastectomy lymphedema (STS) remains a highly lethal entity. Initial surgery, consisting of either wide local excision or amputation, has been associated with the highest rate of long-term survival in STS. As the molecular pathogenesis of these tumors becomes better understood, it is hoped that new methodologies of prevention and management will evolve.

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REFERENCES

1. Petrak JA, Blackwood MM: Axillary dissection: Current practice and technique. Curr Probl Surg 1995;32:312–314.
2. Stewart FW, Treves N: Lymphangiosarcoma in postmastectomy lymphedema. Cancer 1948;1:64–81.
3. Janse AJ, Coevorden FV, Peterse H, et al.: Lymphedema-induced lymphangiosarcoma. Eur J Surg Oncol 1995;21:155–158.
4. Stewart NJ, Pritchard DJ, Nascimento AG, et al.: Lymphangiosarcoma following mastectomy. Clin Orthop 1995;320:135–141.
5. DiSimone RN, El-Mahdi AM, Hazra T: The response of Stewart-Treves syndrome to radiotherapy. Radiology 1970;97:121–125.
6. Schreiber H, Barry FM, Russell WC, et al.: Stewart-Treves syndrome. Arch Surg 1979;114:82–85.
7. Tomita K, Yokogawa A, Terahata S: Lymphangiosarcoma in postmastectomy lymphedema (Stewart-Treves syndrome): Ultrastructural and immunohistologic characteristics. J Surg Oncol 1988; 38:275–282.
8. Kindblom LG, Stenman G, Angervall L: Morphological and cytogenetic studies of angiosarcoma in Stewart-Treves syndrome. Virchows Arch A Pathol Anat Histopathol 1991;419:439–445.
9. Miettinen M, Lehto VP, Virtanen I: Postmastectomy angiosarcoma (Stewart-Treves syndrome). Am J Surg Pathol 1983;7:329–339.
10. Kaufmann T, Chu F, Kaufman R: Post-mastectomy lymphangiosarcoma (Stewart-Treves syndrome): Report of two long term survivals. Br J Radiol 1991;64:857–860.
11. Sandsmark M: Angiosarcoma in post-mastectomy lymphedema. A report of one case of Stewart-Treves syndrome. Ann Chir Gynecol 1977;66:251–253.
12. Yap BS, Yap HY, McBride CM, et al.: Chemotherapy for postmastectomy lymphedema. Cancer 1981;47:853–856.
13. Gill W, Bruce SJ: Stewart-Treves syndrome. J R Coll Surg Edinb 1968;13:34–39.
14. Woodward AH, Ivins JC, Soule EH: Lymphangiosarcoma arising in chronic lymphedematous extremities. Cancer 1972;30:562–572.
15. Martin MB, Kon ND, Kawamoto EH, et al.: Postmastectomy angiosarcoma. Am Surg 1984;50:541–545.
16. Bachulis BL, Old JW, James AG: Postmastectomy lymphangiosarcoma in a patient with carcinoma of the rectum. Am J Surg 1967;113:289–291.
17. Fisher JH: Postmastectomy lymphangiosarcoma in the lymphedematous arm: A review of four cases. Can J Surg 1965;8:350–357.
18. Fitzpatrick PJ: Lymphangiosarcoma and breast cancer. Can J Surg 1968;12:172–177.
19. Barnett WO, Hardy JD, Hendrix JH: Lymphangiosarcoma following post-mastectomy lymphedema. Ann Surg 1969;169:960–968.
20. McSwain B, Whitehead W, Bennett L: Angiosarcoma: Report of three cases of postmastectomy lymphangiosarcoma and one hemangiosarcoma. South Med J 1973;66:102–106.
21. Tragus ET, Wagner DE: Current therapy for postmastectomy lymphangiosarcoma. Arch Surg 1968;97:839–842.
22. Alessi E, Sala F, Berti E: Angiosarcoma in lymphedematous limbs. Am J Dermatopathol 1986;8:371–378.
23. Offori TW, Platt CC, Stephens M, et al.: Angiosarcoma in congenital hereditary lymphedema (Milroy's disease)—Diagnostic beacons and a review of the literature. Clin Exp Dermatol 1992; 18:174–177.
24. Kirchmann TT, Smoller BR, McGuire J: Cutaneous angiosarcoma as a second malignancy in a lymphedematous leg in a Hodgkin's disease survivor. J Am Acad Dermatol 1994;31:861–866.
25. Goette DK, Detlefs RL: Postirradiation angiosarcoma. J Am Acad Dermatol 1985;12:922–926.
26. Baes H: Angiosarcoma in a chronic lymphedematous leg. Dermatologica 1967;134:331–336.
27. Maddox JC, Evans HL: Angiosarcoma of the skin and soft tissue: A study of forty-four cases. Cancer 1981;48:1907–1921.
28. Girard C, Johnson WC, Graham J: Cutaneous angiosarcoma. Cancer 1970;26:868–883.
29. Muller R, Hajdu SI, Brennan MF: Lymphangiosarcoma associated with chronic filarial lymphedema. Cancer 1987;59:179–183.
30. Scully RE, Mark EJ, McNeely WF, et al.: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 18-1993. A 57-year old man with chronic lymphedema and enlarging purple cutaneous nodules of the leg. N Engl J Med 1993;328:1337–1343.
31. Brady MS, Garfein CF, Petrek JA, et al.: Post-treatment sarcoma in breast cancer patients. Ann Surg Oncol 1994;1:66–72.
32. Williams EV, Banerjee D, Dallimore N, et al.: Angiosarcoma of the breast following radiation therapy. Eur J Surg Oncol 1999;25: 221–227.
33. Eby CS, Brennan MJ, Fine G: Lymphangiosarcoma: A lethal complication of chronic lymphedema. Arch Surg 1967;94:223–230.
34. Sordillo PP, Chapman R, Hajdu SI, et al.: Lymphangiosarcoma. Cancer 1981;48:1674–1679.
35. Khodadadeh M, Johnson R, Zeiders GW: Lymphangiosarcoma arising from postmastectomy lymphedema. JAMA 1963;186:131–133.
36. Lambert PB, Frank HA, Bellman S: The role of lymphatic trunks in the response to allogenic skin transplants. Transplantation 1965;3:62–73.
37. Futrell JW, Meyers GH: The regional lymphatics and cancer immunity. Ann Surg 1973;177:1–11.
38. Stark RB, Dwyer EM, DeForest M: Effects of surgical ablation of regional lymph nodes on survival of skin homografts. Ann NY Acad Sci 1960;87:140–148.
39. Mallon E, Posell S, Mortimer P, et al.: Evidence for altered cell-mediated immunity in postmastectomy lymphedema. Br J Dermatol 1997;137:928–933.
40. Kissin MW, Querci della Rovere G, Easton D, et al.: Risk of lymphoedema following the treatment of breast cancer. Br J Surg 1986;73:580–584.
41. Pezner RD, Patterson MP, Hill LR, et al.: Arm lymphedema in patients treated conservatively for breast cancer: Relationship to patient age and axillary node dissection technique. Int J Radiat Oncol Biol Phys 1986;12:2079–2083.
42. Dauway EL, Giuliano R, Haddad F, et al.: Lymphatic mapping in breast cancer. Hematol Oncol Clin North Am 1999;13:349–371.
43. Wilhelm MC, Saul PB, Morgan JA: Post-mastectomy lymphedema. Va Med 1974;101:465–469.
44. Holthofer H, Virtanen I, Kariniemi AL, et al.: *Ulex europaeus* I lectin as a marker for vascular endothelium in human tissues. Lab Invest 1982;47:60–66.
45. Hultberg BM: Angiosarcomas in chronically lymphedematous extremities. Am J Dermatopathol 1987;9:406–412.
46. Benda JA, Al-Jurf AS, Benson AB: Angiosarcoma of the breast following segmental mastectomy complicated by lymphedema. Am J Clin Pathol 1987;87:651–655.
47. Mullick SS, Mody DR, Schwartz MR: Angiosarcoma at unusual sites. A report of two cases with aspiration cytology at unusual sites. Acta Cytol 1997;41:839–844.
48. Capo V, Ozzello L, Fenoglio CM, et al.: Angiosarcomas arising in edematous extremities: Immunostaining for factor VIII-related antigen and ultrastructural features. Hum Pathol 1985;16:144–150.
49. Breiteneder-Geleff S, Soleiman A, Kowalski H, et al.: Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries. Am J Pathol 1999;154:385–394.
50. Jeltsch M, Kaipainen A, Joukov V, et al.: Hyperplasia of lymphatic vessels in VEGF-C transgenic mice. Science 1997;276: 1423–1425.
51. Smith L: Post-mastectomy angiosarcoma: Case report and review of the literature. Tex Med 1984;80:43–44.
52. Kazerooni E, Hessler C: CT appearance of angiosarcoma associated with chronic lymphedema. AJR Am J Roentgenol 1991;156: 543–544.
53. Diaz-Cascajo C, Vega MDL, Rey-Lopez A: Superinfected cutaneous angiosarcoma: A highly malignant neoplasm simulating an inflammatory process. J Cutan Pathol 1997;24:56–60.
54. Dubin HV, Creehan P, Headington JT: Lymphangiosarcoma and congenital lymphedema of the extremity. Arch Dermatol 1974; 110:608–614.
55. Kissin MW, Fisher C, Webb AJ, et al.: Value of fine needle aspiration cytology in the diagnosis of soft tissue tumors: A pre-

liminary study on the excised specimen. Br J Surg 1987;74:479–480.
56. Oettle AG, Blerk PV: Postmastectomy lymphostatic endothelioma of Stewart-Treves in a male. Br J Surg 1963;50:736–743.
57. Hermann JB: Lymphangiosarcoma of the chronically edematous extremity. Surg Gynecol Obstet 1965;121:1107–1115.
58. Lewis JJ, Brennan MF: Soft tissue sarcomas. Curr Probl Surg 1996;33:817–872.
59. Fong Y, Coit DG, Woodruff JM, et al.: Lymph node metastasis from soft tissue sarcoma in adults. Ann Surg 1993;217:72–77.
60. McConnell EM, Haslam P: Angiosarcoma in post-mastectomy lymphoedema: A report of 5 cases and review of the literature. Br J Surg 1959;46:322–327.
61. Pisters PT: Combined modality treatment of extremity soft tissue sarcomas. Ann Surg Oncol 1998;5:464–472.
62. Southwick H, Slaughter DP: Lymphangiosarcoma in postmastectomy lymphedema. Cancer 1955;8:158–160.
63. Hermann JB, Ariel IM: Therapy of lymphangiosarcoma of the clinically edematous limb: Five year cure of a patient treated with intra-arterial radioactive yttrium. AJR Am J Roentgenol 1967;99: 393–399.
64. Brennan MF, Caspers ES, Harrison LB, et al.: The role of multimodality therapy in soft tissue sarcoma. Ann Surg 1991;214:328–336.
65. Harrison LB, Franzese F, Gaynor JJ, et al.: Long term results of a prospective trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. Int J Radiat Oncol Biol Phys 1993;27:259–265.
66. McBride CM, Reeder JW, Smith JL: Angiosarcoma in the lymphedematous limb. South Med J 1969;62:378–380.
67. Naka N, Ohsawa M, Tomita Y, et al.: Prognostic factors in angiosarcoma: A multivariate analysis of 55 cases. J Surg Oncol 1996;61:170–176.
68. Furue M, Yamada N, Takahashi T, et al.: Immunotherapy for Stewart Treves syndrome. J Am Acad Dermatol 1994;30:899–903.
69. Reubi JC, Waser B, Laissue JA, et al.: Somatostatin and vasoactive intestinal peptide receptors in human mesenchymal tumors: In vitro identification. Cancer Res 1996;56:1922–1931.
70. Eary JF, Conrad EU, Bruckner JD, et al.: Quantitative fluorodeoxyglucose positron emission tomography in pretreatment and grading of sarcomas. Clin Cancer Res 1998;4:1215–1220.
71. Lucas JD, O'Doherty MJ, Cronin BF, et al.: Prospective evaluation of soft-tissue masses and sarcomas using fluorodeoxyglucose positron emission tomography. Br J Surg 1999;86:550–556.
72. Steele RJ, Thompson AM, Hall PA, et al.: The *p53* tumour suppressor gene. Br J Surg 1998;85:1460–1467.
73. Donehower LA, Harvey M, Slagle BL, et al.: Mice deficient for p53 are developmentally normal but susceptible to spontaneous tumours. Nature 1992;356:215–221.
74. Zietz C, Rossle M, Haas C, et al.: MDM-2 oncoprotein overexpression, *p53* gene mutation, and VEGF up-regulation in angiosarcomas. Am J Pathol 1998;153:1425–1433.
75. McNamara DA, Harmey JH, Walsh TN, et al.: Significance of angiogenesis in cancer therapy. Br J Surg 1998;85:1044–1045.
76. Folkman J: Tumor angiogenesis: Therapeutic implications. N Engl J Med 1971;285:1182–1186.
77. Ferrara N: The role of vascular endothelial growth factor in pathological angiogenesis. Breast Cancer Res Treat 1995;36:127–137.
78. Hashimoto M, Ohsawa M, Ohnishi A, et al.: Expression of vascular endothelial growth factor and its receptor mRNA in angiosarcoma. Lab Invest 1995;73:859–863.
79. Billingsley KG, Burt ME, Jara E, et al.: Pulmonary metastases from soft tissue sarcoma. Ann Surg 1999;229:602–612.